The Office asserts that:

> The terms such as 'for example water' and 'especially' render Claim 22 indefinite.
>
> 'Fine' in file pored filter in claim 24 is indefinite; fine is a relative term. Applicant's arguments that the term is known in the art are not found to be persuasive since no evidence is presented to show that pores of 1-200 nm are considered as fine pores.
>
> The amendment to claim 33 did not cure the deficiency. This claim is dependent from claim 22 and claim 22 does not recite a lyophilisate. How is this lyophilisate prepared and from where?
>
> Claim 52 is not further limiting claim 31 in terms of pore size. Applicant has not addressed this issue sufficiently. The upper limit of the pore size recited in claim 52 is 0.15 whereas the upper limit in claim 31 is 0.8.

Applicants respectfully submit that the claims have been amended to overcome these rejections.

Regarding the Office's assertion that claim 52 is not further limiting of claim 31 in terms of pore size, Applicants respectfully disagree. Claims 31 and 52 read as follows:

> 31. The method of claim 22, wherein the formation of the transfersomes is brought about by filtration and the filter material used in said filtration has a pore size of 0.01 μm to 0.8 μm.
>
> 52. The method of claim 31, wherein the formation of the filter material has a pore size of 0.08 μm to 0.15 μm.

The range 0.01 μm to 0.8 μm is broader than the range 0.08 μm to 0.15 μm. The lower limit 0.01 μm is less than the lower limit 0.08 μm. Further, the upper limit 0.8 μm is greater than the upper limit 0.15 μm. Thus, the range 0.08 μm to 0.15 μm is both greater in lower limit ($0.08 < 0.01$) and less in upper limit ($0.15 < 0.8$).

It is respectfully submitted that all the claims comply with 35 U.S.C. §112. Reconsideration and withdrawal of the rejections is respectfully requested.

2. 35 U.S.C. §102 Rejections

Claims 22-33 have been rejected under 35 U.S.C. §102(b) as being anticipated by EP 0 475 160 of record.

The Office asserts:

> EP discloses instant composition containing a drug, an amphiphilic lipid and a surfactant in instant amounts and a method of preparation (see the entire document).

Applicants respectfully traverse.

Applicants claim, in claim 22, a method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal. The method comprises the following steps:

a. selecting a first amphiphilic lipid component
b. selecting a second amphiphilic lipid component and selecting at least one active ingredient or
   selecting an amphiphilic active ingredient to form a second amphiphilic lipid component, and optionally selecting one or more further active ingredients
c. selecting the first and second amphiphilic lipid components so that the solubility of the second amphiphilic lipid component in a pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in the medium
d. adapting the composition or concentration of the preparation for transport through skin or mucous membrane, by adjusting the content of the more soluble component to less than 0.1 mole percent of the content of the first and second amphiphilic lipid components at which the enveloped droplets stabilize, if there is a solubilizing point
e. adjusting the content of amphiphilic lipid components, such that the ratio of the permeation capability relative to reference particles, wherein the reference particles are water, which are much smaller than the constrictions of the test barrier, is between 10^{-5} and 1
f. producing a transfersome suspension by means of applying energy to the mixture of said amphiphilic lipid components including at least one active ingredient, said transfersomes comprising liquid droplets encompassed within a sheath comprising said amphiphilic lipid components, said amphiphilic lipid components being selected such that said transfersomes are capable of undergoing sufficient deformation to pass through said skin

or mucous membrane without being solubilized, said active ingredient being contained in said liquid droplets, or in said sheath, or in both said liquid droplets and said sheath.

There are two alternatives set forth in claim 22: (1) where there is no solubilization point and (2) where there is a solubilization point.

EP 0 475 160, which corresponds to US 6,165,500, is very different. First, only one situation is considered, namely, that the system defined has a solubilization point. In other words, these references only address systems where the amount of surfactant can be gradually increased until, at some concentration, the system becomes incapable of forming transfersomes. Above this concentration, you will only get micelles, which are not stable on any relevant time scale and do not provide the kind of membranes which characterize liposomes and, thus, transfersomes.

Further, these references make it very clear that the amount of surfactant added, to render the membrane flexible and, thus, the whole vesicle a transfersome, must be between 0.1 and 99 mol-% of that amount of surfactant which characterizes the solubilization point. In other words, there is an amount of surfactant that characterizes the solubilization point. The amount of surfactant in the system must not exceed 99 mol-% of this amount because if it does, solubilization is approached and the system becomes unstable even in the best case scenario.

The teaching of the present invention is entirely different. In one alternative, there is no solubilization point at all, i.e. it does not matter how much surfactant you add, you never solubilize the system. This is not even contemplated by the cited references. In the other alternative, the present invention teaches systems where there is indeed a solubilization point, but the phenomenon of membrane destabilization, which produces transfersomes, surprisingly occurs at very low amounts of surfactant. These amounts are less than 0.1 mol-% of the amount of surfactant which would indeed cause solubilization.

Thus, the cited references teach that the amount of surfactant added to produce a transfersome must be between 0.1 and 99 mol-% of that amount of surfactant which characterizes the solubilization point. Further, the cited references teach approaching this solubilization point as closely as possible while maintaining sufficient stability (see, e.g. EP '160 translation claim 1). The present invention, on the other hand, teaches that flexibilization of the membrane is achieved at amounts less than 0.1 mol-% of the solubilization point. The cited references do not achieve membrane flexibilization at all at such low amounts but, rather, at much higher amounts preferably approaching 99 mol-% of the solubilization point.

Further, regarding the Office's assertion that:

> With regard to the more than 0.1 and 99 mol % in the prior art and the instant 'less than 0.1 and 99 mol %', the examiner points out to claim 1 of US equivalent which recites 5.5:1 to 1:500 and it would appear that instant broad range falls within this range.

Applicants respectfully submit that claim 1 of US '500 states "the ratio of lipid to surfactant is from about 5.5:1 to about 1:500". This ratio defines a completely different type of relationship than that set out by Applicants. Namely, Applicants teach that the amount of surfactant added to produce a transfersome is less than 0.1 mol-% of that amount of surfactant which characterizes the solubilization point. Thus, Applicants respectfully submit that the ratios pointed to by the Office do not correspond to those defined by Applicant.

As provided in MPEP-2131, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Or stated another way, "The identical invention must be shown in as complete detail as is contained in the ... claims. *Richardson v Suziki Motor Co.*, 868 F.2d 1226, 9 USPQ 2d. 1913, 1920 (Fed. Cir. 1989). Although identify of terminology is not required, the elements must be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

It is clear from the foregoing remarks that the above-identified claims are not anticipated by the cited reference. In particular, the cited reference fails to describe a method wherein the amount of surfactant added to produce a transfersome is less than 0.1 mol-% of that amount of surfactant which characterizes the solubilization point or wherein there is no solubilization point.

Accordingly, reconsideration and withdrawal of the 35 U.S.C. §102 rejections is respectfully requested.

3. 35 U.S.C. §103 Rejections

Claims 22-33 and 49-90 have been rejected under 35 U.S.C. §013(a) as being unpatentable over EP 0 475 160 cited above.

> As pointed our above, EP teaches a composition containing a drug, an amphiphilic lipid and a surfactant in instant amounts and a method of preparation. It is unclear whether the reference teaches all the instant functional parameters. In case they are different, in the absence of showing the criticality, they are deemed to be parameters manipulatable by an artisan to obtain the best possible results.

Applicants respectfully traverse for the reasons set forth above. Namely, the cited reference and the corresponding US case fails to describe a method wherein the amount of surfactant added to produce a transfersome is less than 0.1 mol-% of that amount of surfactant which characterizes the solubilization point or wherein there is no solubilization point.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). MPEP 2142.

As set forth above, the cited reference and the corresponding US case fails to teach or suggest all of the claim limitations. Further, there is no motivation to modify the references as required by the claims. Rather, the references specifically teach to add a large amount of surfactant such that the composition approaches the solubilization point. As set out, an amount of surfactant added to the composition will result in the solubilization point. The reference teaches to approach this amount as closely as possible, i.e. to approach 100 mol-% of the amount of surfactant which characterizes the solubilization point) (see, e.g. EP '160 translation claim 1). Thus, the present invention teaches that the amount of surfactant added is less than 0.1 mol-% of the amount of surfactant which characterizes the solubilization point. On the other hand, the reference states that the amount of surfactant is between 0.1 and 99 mol-% and specifically teaches to approach the 99 mol-% limit as closely as possible. Thus, there is absolutely no motivation to modify the reference such that the amount of surfactant added is less than 0.1 mol-%. Rather, the exact opposite is taught.

Thus, it is clear from the forgoing that the above-identified claims are not obvious over the cited reference. Accordingly, reconsideration and withdrawal of the 35 U.S.C. §103 rejections is respectfully requested.

CONCLUSION

Reconsideration and allowance of claims 22-33 and 49-93 is respectfully requested in view of the foregoing discussion. This case is believed to be in condition for immediate allowance. Applicant respectfully requests early consideration and allowance of the subject application.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

Respectfully submitted,

Date: May 2, 2003

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#332052

VERSION WITH MARKINGS TO SHOW CHANGES MADE IN CLAIMS

Please note that additions to the claims are shown underlined and deletions are shown in brackets.

Please amend claims 22, 24 and 33 as follows:

22. A method for producing a preparation for transporting at least one active ingredient through the skin or mucous membrane of a mammal comprising:

a. selecting a first amphiphilic lipid component; and

b. selecting a second amphiphilic lipid component and selecting at least one active ingredient; or

c. selecting an amphiphilic active ingredient to form a second amphiphilic lipid component, and optionally selecting one or more further active ingredients;

d. said first and second amphiphilic lipid components being selected so that the solubility of the second amphiphilic lipid component in a pharmaceutically acceptable suspending medium is at least ten times greater than the solubility of the first amphiphilic lipid component in said medium;

e. adapting the composition or concentration of the preparation for transport through skin or mucous membrane, by adjusting the content of the more soluble component to less than 0.1 mole percent of the content of the first and second amphiphilic lipid components at which the enveloped droplets stabilize, if there is a solubilizing point; and

f. adjusting the content of amphiphilic lipid components, such that the ratio of the permeation capability relative to reference particles which are much smaller than the constrictions of the barrier, [for example] <u>wherein the reference particles are</u> water, is between 10^{-5} and 1[, especially between 10^{-2} and 1];

g. producing a transfersome suspension by means of applying energy to the mixture of said amphiphilic lipid components including at least one active ingredient, said transfersomes comprising liquid droplets encompassed within a ssheath comprising said amphiphilic lipid components, said amphiphilic lipid components being selected such that said transfersomes are capable of

undergoing sufficient deformation to pass through said skin or mucous membrane without being solubilized, said active ingredient being contained in said liquid droplets, or in said sheath, or in both said liquid droplets and said sheath.

24. The method of claim 22 wherein stability and permeation capability are determined by filtration under pressure through a [fine-pored] filter <u>having pore size ranging from about 30 to about 100 nm</u> or by controlled mechanical whirling up, shearing or comminuting.

33. The method of claim 22, wherein shortly before use, the enveloped droplets are prepared from a concentrate [of] <u>or</u> lyophilisate.

Please add the following new claims:

91. The method of claim 90, wherein the ratio of the permeation capability relative to reference particles which are much smaller than the constrictions of the test barrier is between 10^{-2} and 1.

92. The method of claim 22, wherein the transfersomes are produced by a method selected from the group consisting of filtration, treatment with ultrasound, stirring and shaking